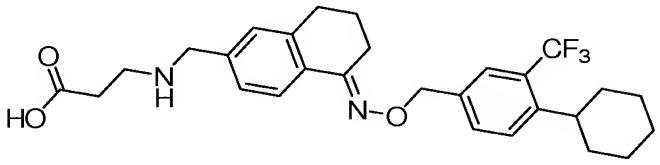
REMARKS/ARGUMENTS

Claims 1-10 are pending in this application. Claims 11 and 12 have been canceled, without prejudice, in an effort to expedite the prosecution of this application. Claims 1-6, 9 and 10 have been amended.

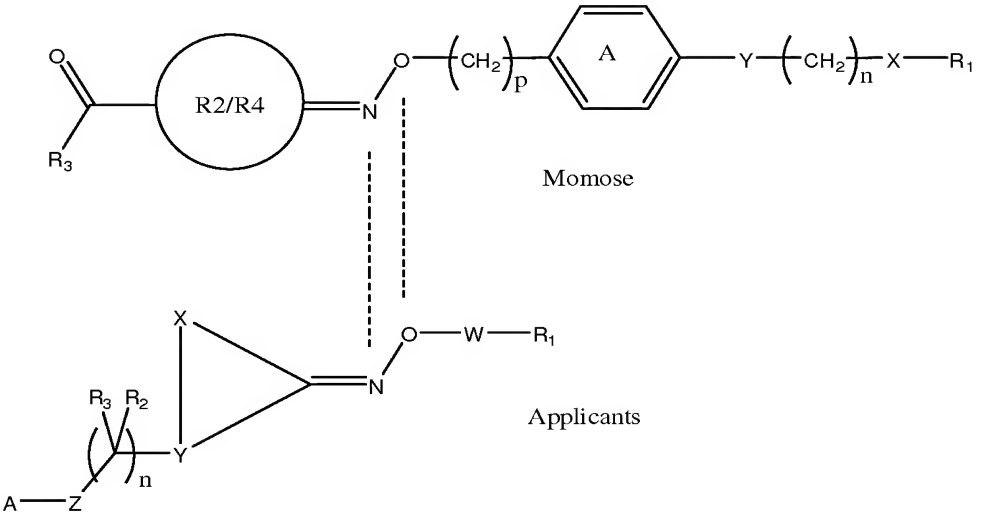
Election/Restriction

In response to an election of species request by the Examiner on May 27th, 2009, Applicants affirm their election of the compound which is Example 1 on page 22 of the application as species, namely 3-{[5-(4-Cyclohexyl-3-trifluoromethyl-benzyloxyimino)-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl]-amino}-propionic acid, having the structure:



In addition to the compound of Example 1 on page 22, this is the first compound listed in paragraph 32, page 7 of the specification and the first compound listed in claim 7, page 35. The claims readable on the elected species include claims 1-12.

The Examiner states that claim 1 lacks unity of invention because the species from claim1 highlighted by the Examiner require the technical feature of a bicyclic oxime but this technical feature does not make a contribution over the prior art in view of US 6,251,926 (Momose). The Applicants respectfully disagree with the Examiner as Momose does not describe many of the key groups of the Applicant's Markush. Consider the following comparison:



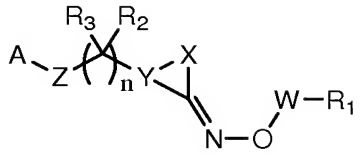
There are many differences between the Markush in Momose and that of the Applicants. For example, Momose has no definition for the R^2-R^4 ring formation and there is no disclosed example of a ring formed by R^2 and R^4. The two preferred embodiments of Momose, shown in column 15, show m = zero and, therefore, R^4 would not be present to form a ring with R^2. Further, Momose has a carbonyl group directly attached to the R^2-R^4 ring. The Applicants Markush can never have a carbonyl attached to the bicyclic ring because even with n = zero, Z has to be a minimum of $-CH_2-$. Further, Y in Momose is not present in the Applicants Markush as Y is selected from O, $S(O)_{0-2}$ and NR^7. For R_1, the Applicants have two rings directly connected to each other such as cyclohexyl and phenyl. In comparison, the Y group of Momose is selected from O, $S(O)_{0-2}$ and NR_7.

Therefore, the Applicants submit that the claims have a special technical feature that has a contribution over the prior art. Further, the international searching authority, in their written opinion mailed on 29 June 2005, did not find a lack of unity. In view of the foregoing, Applicants respectfully request that the restriction requirement based on lack of unity of invention be withdrawn and all the claims be examined on their merits.

Specification

The Applicants submit the following abstract according to MPEP §608.01(b):

"The invention provides a novel class of cyclic oximes of Formula I:



wherein A, X, Y, Z, W, R_1, R_2, R_3 and n are as described in the Summary of the Invention; useful in the treatment or prevention of diseases or disorders mediated by lymphocyte interactions, particularly diseases associated with EDG receptor mediated signal transduction."

Claims Rejections – 35 USC §101

The Examiner has rejected claim 11 under 35 USC 101. The Applicants have canceled claim 11. Applicants respectfully request that the Examiners rejection based on claim 11 be withdrawn.

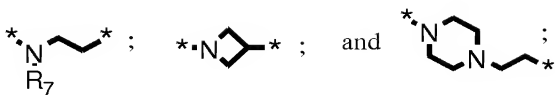
Claims Rejections – 35 USC §112

The Examiner has rejected claims 1, 9 and 11 under 35 USC 112 as being indefinite. Applicants have canceled claim 11. Applicants have amended claim 1 to delete the phrase "hydrates, solvates, isomers and prodrugs" and claim 9 "animal" has been replaced with "human". Support for this amendment can be found in paragraph 39 "[a]n indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 100 mg…".

The Examiner has rejected claims 1-12 under 35 USC 112 as being indefinite. Claims 11 and 12 are canceled. The Applicants have amended claims 1 to 6.

Claim 1 has been amended such that X is only C_{2-4}alkenylene; wherein one methylene group of X can be replaced with an –O– atom. Support for this amendment can be found in the examples. The Examiner has pointed out that W can be $-(CH_2)_2$ or $-(CH_2)_3$- but the specification is also enabling in situations where a methylene of X can be replaced with an oxygen atom as shown in examples 3 (page 23) and examples 15-21 (table 1, pages 26/7). Claim 1 has also been amended such that W is only methylene. Support for this amendment can be found in all 21 examples in the specification.

Claim 2 has been amended to include only the three divalent radicals shown:



1 2 3

Support for these divalent radicals can be found in the examples. Divalent radical 1 is found in: example 1, page 22; example 3, page 22; example 6, page 24; and examples 9, 10, 11, 13, 14, 16, 18 and 21 of table 1 starting on page 25. Divalent radical 2 is found in: example 2, page 22; example 5, page 24; and examples 7, 8, 12, 17, 19 and 20 of table 1, starting on page 25. Divalent radical 3 is found in example 4 on page 23.

Claim 10 has been amended in accordance with the Examiner's suggestions. Support for "breast cancer" can be found in the specification in paragraph 38, page 10: "[f]urthermore, the compounds of formula I are useful in cancer chemotherapy, particularly for cancer chemotherapy of solid tumors, e.g. breast cancer, or as an anti-angiogenic agent."

Claims Rejections – 35 USC §103

The Examiner has rejected claims 1-12 under 103(a) as being obvious over US 2009/0036423 (Pan) in view of 5,674,879 (Manning) and further view of Mu et al (J. Med. Chem. 2002, 45, 4774-4785). Claim 11 and 12 are canceled.

The Examiner has stated that Pan constitutes prior art only under 35 USC 102(e). However, the Pan reference does not describe the Applicants invention, a requirement of 102(e), and therefore Pan cannot be a 102(e) reference cited against the instant claims.

In ascertaining the differences between Pan and the instant claims, the Examiner has focused on two differences between the applications. However, in addition to the Examiners stated differences, the oxime in Pan is linked directly to the Y ring whereas the oxime of the instant claims is linked to Y via a CR_2 group, where R_2 can be hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or halo-substituted-C_{1-6}alkyl (Pan exemplifies R_2 as methyl). This CR_2 group is not a difference of the successive addition of the same chemical group because the CR_2 group is not present in Pan et al. Therefore, contrary to the Examiner's assertion, the subject matter does not overlap when "n" is one and Pan does not teach the Applicant's invention.

In comparing the differences with Y, the Examiner states that the act of conformationally restricting functional groups in biological molecules is well known in the art and quotes Manning as teaching the general concept. However, Manning is discussing

conformationally restricting known peptidic compounds that have angiotensin properties (see column 1). Manning is hypothesizing that compounds which conformationally restrict the possible orientations of the pharmacaphores incorporated therein may maximize the interaction between those pharmacaphores and the binding site of the angiotensin II receptor subtype or subtypes of interest. Specifically, Manning has designed conformationally restricted angiotensin II antagonists by incorporating a biphenyl radical to form a more rigid special relationship between two heterocyclic rings and all the examples in Manning have a biphenyl ring system. Manning specifically teaches incorporation of biphenyls for angiotensin II receptor antagonists but does not show, comparatively, the effect on biological activity with or without the biphenyl group. Manning's specific teaching does not qualify as teaching a general concept of conformationally restricting functional groups in biological molecules to one of ordinary skill in the art.

The Examiner further states that Mu et al teaches conformational restriction that can be accomplished upon incorporation into a bicyclic ring but Mu describes analogues of Lavandustin A (which have antiproliferative activity) and states "surprisingly, the results indicated very little effect of conformational restriction on biological activity". In effect, Mu teaches away from the use of conformational restriction as a way of enhancing biological activity.

In summary: Pan does not teach the present invention; Manning does not teach a general concept of conformationally restricting functional groups in biological molecules; and Mu teaches surprisingly little effect on biological properties of conformational restriction in the context of protein tyrosine kinases. The Applicants, therefore, would not have been motivated to use the teachings of either Manning or Mu in the design of their molecules in the context of EDG receptor activity.

Double Patenting

The Examiner has provisionally rejected claims 1-11 on the ground of non statutory obviousness-type double patenting as being unpatentable over copending Application Pan et al, in view of manning and Mu. For the reasons stated above, the Applicants believe the instant claims are patentable and respectfully request that the Examiners rejection based on double patenting be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned attorney at 858-812-1796.

In the event that the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-1885** referencing docket No. **PAT033678-US-PCT**.

Respectfully submitted,

/Scott W. Reid, Reg. No. 48,097/

Scott W. Reid, D.Phil.
Reg. No. 48,097
Agent for the Applicants

The Genomics Institute of the
Novartis Research Foundation (GNF)

Date: November 20, 2009

Customer No. 29490

IPLegal@gnf.org
Phone: (858) 812 1796
Fax: (858) 812 1909